# Advantages And Disadvantages of Different COVID-19 Vaccines

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**Abstract.** After the outbreak of the epidemic, countries around the world have begun intensive research and development of vaccines. Theoretically, all existing vaccine types and technologies can be applied to COVID-19 vaccine research. More than 100 COVID-19 vaccine projects registered on the official website of WHO include these three generations of different types of vaccines. At present, 16 vaccines have entered clinical trials, five of which are from China, including two inactivated vaccines under China Biotechnology Co., Ltd. (hereinafter referred to as "China Biotechnology"). Most of these vaccines are still in phase I. This article will introduce inactivated vaccine, Ad5-nCoV Adenovirus vector COVID-19 vaccine, RBD CHO vaccine and nucleic acid vaccine in detail. The different vaccines have different advantages due to the different ways of working. At the moment when the COVID-19 vaccine has been launched, personal protection and cutting off the transmission route of COVID-19 are still the most important ways to protect oneself and prevent the spread of the epidemic.

**Keywords:** COVID-19, Vaccines, Advantages.

## 1. Introduction

Today, the new coronavirus pneumonia (COVID-19) (hereafter referred to as COVID-19), which is prevalent around the world, has caused great disasters to human society. COVID-19 is a new coronavirus emerging in 2019 [1]. Coronavirus is a single-stranded positive-stranded RNA virus with a capsule, most of which are spherical in shape, with a diameter of about 60-200 nm. Its envelope has regular arrangement of spiny protrusions, similar to the shape of a crown, so it is named coronavirus [2]. The coronavirus has the longest known RNA virus nucleic acid chain. Its genome includes the coding genes for numerous structural proteins in addition to the genes for associated enzymes. Spike (S protein), membrane (M protein), envelope (E protein), and nucleocapsid (N protein) proteins are predominantly encoded by genes that are tightly linked to viral RNA. S protein mediates virus invasion and regulates the species and tissue specificity of virus infection; E protein and M protein primarily take part in the assembly process of the virus; N protein packages the genome to form nucleoprotein complex. S protein contains host cell receptor recognition sites [3].

The most effective strategy to manage the outbreak is to immediately create a vaccine against COVID-19 because no medications with definite therapeutic effects on COVID-19 have yet been discovered. According to different technical paths, the main strategies of COVID-19 vaccine R&D at present include inactivated vaccine, adenovirus vector vaccine, RBD vaccine, nucleic acid vaccine, etc [1].

## 2. Difference of COVID-19 vaccines

### 2.1. Inactivated vaccine

The inactivated vaccine is produced by Beijing Institute of Biological Products of China Pharmaceutical Group Co., Ltd Liability company, Wuhan Institute of Biological Products Co, Ltd Beijing Kexing Zhongwei Biotech Co, Ltd [4]. The first step is to get live virus samples from patients who are already infected, Vero cells are used to achieve virus number growth. β- Proprolactone is used to invalidate the viruses by combining with the gene of COVID-19, but the spike protein is still effective. Researchers add trace aluminum base compound (as an adjuvant to stimulate the immune

system) to the viruses. After injecting into the body, those invalid viruses are engulfed by immune cells named antigen-presenting cell. Antigen-presenting cells degrade COVID-19 and display a segment of the virus on the cell surface, so that helper T cells can recognize this segment and activate T cells to generate an immune response.

Its advantages are simple and fast preparation methods and high safety. Its disadvantages are large vaccination dose, humans need to inoculate 2 doses; The recommended time between immunization doses is three weeks or less, and the second dose should be given as soon as feasible within eight weeks. Also, it triggers a short immunization period and a single immunization route. Its most terrible disadvantage is that it sometimes causes an increase in antibody dependence. The strong effect (ADE) will aggravate the virus infection, which will lead to serious adverse reactions caused by the failure of vaccine research and development.

### 2.2. Ad5-nCoV Adenovirus vector COVID-19 vaccine

Researchers integrate the gene sequence encoding the S protein of COVID-19 into the adenovirus genome through gene recombination to become replication-defective adenovirus vector vaccine. After amplification, purification, and addition of an appropriate adjuvant, the finished vaccine is made. After the human body is inoculated with the vaccine, it can rapidly enter the cell with the help of the strong infective ability of the adenovirus vector, release the gene sequence encoding S protein in the cell for S protein synthesis, and become an antigen that can be recognized by the body. Adenovirus vectors are divided into replication type and replication defect type. At present, the replication defect type is commonly used. The replication defect type retains the complete structure and infectivity of adenovirus, but the self-replication ability is lost, which is safer. The replication defect type will be metabolized by the body. This type of vaccine works more efficiently due to two reasons. One is the adenovirus we used has strong infectivity. Adenovirus is a linear double-stranded DNA virus. It has a wide host range and low pathogenicity in humans. because it can activate humoral immunity and cellular immunity at the same time. The advantage of this kind of vaccine is that it has a strong immune effect. As a foreign substance, the virus itself can stimulate an immune response, so it can achieve a good immune effect without adding an immune adjuvant. Secondly, it is convenient to administer the vaccine. This type of vaccine can be delivered orally, intravenously, topically, orally, and intradermally. The single antigen target of this type of vaccine is a drawback. Most of the COVID-19 adenovirus vector vaccines currently developed use the S protein of COVID-19 as the target. There is a lack of research on other targets or joint targets. Whether the vaccine can induce the body to produce sufficient immune protection is still uncertain. In addition, the biggest problem of the adenovirus vector vaccine is how to overcome the so-called "pre-storage immunity", because the widely used adenovirus vectors are human serum adenovirus AdHu2 and AdHu5, and there are neutralizing antibodies against human serum adenovirus in the human body. After the injection of the vaccine, the antibodies in the body will directly attack the adenovirus, thus reducing the efficacy of the vaccine. High-dose immunization can improve the immune efficacy, However, there may be carrier toxicity problems The advantages of adenovirus vector vaccine are: safe, efficiency and less adverse reactions.

### 2.3. RBD CHO

The recombinant subunit vaccine is the recombinant COVID-19 vaccine (CHO cell) produced by Anhui Biological Pharmaceutical Co., Ltd. The idea is to recombine the receptor binding region (RBD) gene of the COVID-19 S protein into the gene of Chinese hamster ovary (CHO) cells, express it in vitro to create an RBD dimer, and then add aluminum hydroxide adjuvant to increase immunogenicity.

### 2.4. Nucleic acid vaccine

#### 2.4.1 DNA

The nucleic acid vaccine of COVID-19 can be divided into DNA vaccine and mRNA vaccine. The nucleic acid vaccine is known as the following whole-virus vaccine and recombinant subunit disease [1].

The "third generation vaccine" after the vaccine, including DNA vaccine and mRNA vaccine, is a promising new-generation vaccine research and development technology [5].

The basic idea behind a DNA vaccine is to create a vaccine from DNA that codes for an antigen protein, administer it to a recipient, and allow the antigen to be expressed in order to trigger an immune response in the body and provide the recipients with the potential to prevent disease. The COVID-19 DNA vaccine will assist the body create memory T and B cells after inoculation. However, there may be the following safety problems: First, the recombinant plasmid needs to enter the nucleus for transcription, which will increase the risk of integration of foreign genes into human chromosomes; Secondly, theoretically, DNA vaccine may stimulate the body to produce anti-DNA antibodies related to autoimmune diseases, leading to autoimmune diseases. Third, because DNA vaccine will continue to produce a small amount of antigen, which may lead to tolerance, especially in children with the immature immune system. DNA vaccine has been used for research on HIV, influenza virus, malaria, hepatitis B virus, etc. in the early stage, but it has not been used for human disease prevention before.

#### 2.4.2 mRNA vaccines

The use of mRNA in the clinical setting began in 1990 with Wolff et al. In order to achieve the goal of clinical treatment, mRNA technology first synthesizes mRNA by in vitro transcription technology, transports it into the human body using the proper delivery method, and then relies on the cell's own translation mechanism to convert it into the target protein. Compared with the technology based on DNA and virus vectors, mRNA technology has many advantages as follows:

(1) High efficiency: once the mRNA reaches the cytoplasm, it will be translated immediately, instead of entering the nucleus to function;

(2) Safety: mRNA will not be integrated into the genome, and there is no risk of insertion mutation; mRNA has only transient activity and can be completely degraded through physiological metabolic pathways. Unlike vaccines based on viral vectors, the human body will not have immunity to mRNA vaccine vectors;

(3) Controllable quality: because the mRNA encoding different antigens is highly similar in chemistry and physics, the formulation design and manufacturing process of the new mRNA vaccine follow the same steps, and the mRNA production process is relatively simple and the quality is controllable.

S protein is one of the main structural proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It contains two subunits of S1 and S2 protein. The specific receptor binding domain (RBD) in the S1 subunit is the key region of S protein binding to ACE2 receptor on the surface of a host cell, and S2 drives the fusion of the virus and host cell membrane. S protein is the main target of neutralizing antibodies (Abs) after virus infection. In addition, immunogenic CD4 and CD8 T cell epitopes are mainly located in the structural proteins of the virus, especially the S protein [2]. Therefore, S protein is the main target of vaccine antigen selection.

Whether to choose full-length S protein or RBD region as the target antigen of the COVID-19 vaccine design? BioNTech initially designed mRNA COVID-19 vaccine candidate products, including BNT162b1 containing RBD coding gene and BNT162b2 containing full-length S protein-coding gene. Phase I/II clinical study data showed that the SARS-CoV-2 antigen-specific T cell reaction recognition epitopes of subjects vaccinated with the BNT162b2 vaccine were more extensive than those of BNT162b1. BNT162b2 can induce high-strength CD4+and CD8+T cell responses at the same time. BNT162b2 causes T cells to react to the rest of the S protein regions that are not included in RBD and BNT162b1 vaccines, while the immune recognition ability for more the S-protein T cell epitopes may have the potential to produce a more consistent response in different

populations and the elderly. In addition, BNT162b2 has better overall tolerance, generally mild to moderate and transient (1-2 days) systemic events, such as fever, fatigue and chills, without serious adverse events. Compared with BNT162b1, BNT162b2 has similar immunogenicity, but better tolerance. Therefore, BNT162b2 was selected to enter the phase 3 clinical trial and listed in many countries and regions in the world [6].

### 2.5. Key factors of mRNA vaccine design

Because mRNA is extremely easy to be degraded, ensuring the stability of mRNA will also ensure its expression effect. Many factors will affect the stability and protein expression of mRNA in cells, such as the selection of 5'UTR or 3'UTR, the secondary structure of mRNA, the optimization of Poly (a) tail, the optimization of mRNA codon, the selection of modified nucleotides, etc.

Kariko et al. found that when the naturally existing modified nucleoside, such as pseudouridine （Ψ) When 5-methylcytidine (m5C) and N6-methyladenosine (m6A) are mixed into mRNA, the amount of mRNA translation is about 10 times that of unmodified mRNA. Other studies indicated that modified nucleoside could inhibit RNA degradation; mRNA modified with pseudouridine has higher translation efficiency and longer half-life. At present, the most commonly used method is to add modified nucleotides into the mRNA molecule, which can significantly improve its translation efficiency and stability, and extend its half-life.

### 2.6. Sequence optimization

Sequence modification of mRNA can improve the stability of mRNA and protein expression. The sequence optimization strategy can improve the efficiency of mRNA translation, enhance its stability, and improve the efficiency of recombinant protein production and the rate and efficiency of protein transformation. Sequence optimization may also change the transformation kinetics and may lead to changes in protein conformation. RNActive technology can improve translation efficiency, delay the decay of mRNA, and modify mRNA by enriching the content of guanine and cytosine (GC) in the readable frame (ORF) of mRNA, and introducing regulatory elements [UTR and poly (A) tail of non-translation region]. The mRNA designed by this technology is composed of conventional nucleic acids without nucleoside modification. In order to enhance its immune stimulation ability, part of the mRNA in this method forms a stable complex with protamine. Therefore, the final vaccine consists of two parts: naked mRNA and mRNA-protamine complex. After injection of the vaccine, naked mRNA is used as a translation template, while protamine mRNA complex stimulates strong Toll-like receptor (TLR) activation.

### 2.7. 5'end cap nucleic acid base modification

The 5 'end cap can promote the stability of mRNA in translation, splicing, polyadenylation, and derivation from the nucleus, and endow the in vitro transcriptional mRNA with resistance to cytolytic enzymes, thus extending the half-life of mRNA. The structure and effective performance of the 5 'cap affect the synthesis of protein, thus affecting the expression of antigen that can stimulate immune response.

### 2.8. 3'Poly (A) tail modification

Poly (A) tail, which has repetitive adenosine residues at the 3 'end, is an important factor affecting the efficiency and stability of mRNA translation. The degradation of mRNA in eukaryotes begins with the deadenylation of poly (A) tail by exonuclease. In the cytoplasm, Poly (A) tail combines with PABP (poly (A) binding protein) to enhance the stability of mRNA. At the same time, PABP can combine with translation initiation factors to enhance mRNA translation.

### 2.9. UTR modification

The 5 'and 3' UTR elements on the flanks of the mRNA coding sequence affect the stability and translation of mRNA, both of which are key issues in vaccine design. These regulatory sequences can

significantly increase the half-life and expression of therapeutic mRNA. For example, Tanguay et al. found that mRNA carrying 3'UTR increased mRNA expression by 51 times. In addition, increasing the length of 3'UTR increased the stability of reporter gene mRNA by 2.5 times.

### 2.10. Antigen delivery system: lipid nanoparticles

Another important issue is how to ensure the smooth entry of the mRNA vaccine into the cytoplasm to initiate translation - mRNA must not only pass through the cell membrane but also not be hydrolyzed by the extracellular RNA enzyme [6]. Therefore, a good delivery system can protect the effective entry of mRNA into human cells without being damaged, and can also effectively improve targeting and bioavailability. At present, the delivery system of mRNA can be divided into two categories, namely lipid or lipid delivery system and polymer delivery system. Lipid nanoparticles (LNP) is one of the most commonly used delivery systems. Different lipid components used in nanoparticles may affect the amount of mRNA entering cells.

## 3. Difference of three mRNA COVID-19 vaccines and their protection in the real world

### 3.1. Main differences between the three mRNA vaccines

BNT162b2 and mRNA-1273 replace uridine with pseudouridine through nucleoside modified mRNA technology, which can avoid the recognition of mRNA by pattern recognition receptors (such as TLR receptors TLR3 and TLR7) and activate natural immunity, thus increasing the efficiency of mRNA. CVnCoV increases the immunogenicity and stability of mRNA by RNActive technology of changing the sequence of mRNA. In addition, different mRNA vaccines have different doses (from 12 μ G to 100 μ g), its security and effectiveness will also be different [7].

### 3.2. The protective power of mRNA vaccine in the real world

In a real-world study on the efficacy of BNT162b2 and mRNA-1273 vaccines, 80% of 3975 participants received at least one dose of mRNA vaccine. The results of this study showed that the effective rate of mRNA-1273 and BNT162b2 was 82% and 93% respectively after complete inoculation of mRNA vaccine [8]. At present, BNT162b2 vaccine has accumulated relatively rich real-world data, and the overall effectiveness of the vaccine is 89-95.3%. In the face of the global outbreak of the COVID-19, mRNA technology is widely used in the research and development of COVID-19 vaccine [9]. The effectiveness and safety of the mRNA COVID-19 vaccine developed and produced by BioNTech and Moderna once again demonstrated the feasibility of mRNA technology for disease prevention. With the in-depth study of mRNA, potential therapeutic targets of diseases and delivery systems in the future, mRNA technology is expected to be a new method for treating genetic diseases, cancer, infectious diseases and other diseases [10].

## 4. Conclusion

The research and development cycle of traditional vaccines is generally 10-15 years, and COVID-19 vaccine will enter the 'phase of clinical trials and even emergency use or conditional marketing in less than one year. On the one hand, this is the result of the joint efforts and cooperation of countries in the face of COVID-19, but it is also necessary to see that there is still a lot of basic research work to be further improved after the launch of COVID-19 vaccine, for example, due to the short duration of clinical trials and limited sample population, The rate of rare adverse reactions and the long-term protection effect remain to be observed; The impact of COVID-19 vaccination on the condition of patients with existing basic diseases has not been systematically studied; As a single strand positive strand RNA virus, whether the high variability of COVID-19 affects its infection mechanism and immune response, and whether existing vaccines can produce immune efficacy against its mutant

strains, are all questions to be further studied. At present, personal protection and cutting off the transmission route of COVID-19 are still the most important ways to protect oneself and prevent the spread of the epidemic.

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